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(22) Datum prijave (*Application Date*):

23.1.2004 (23.jan.2004)

(21) Številka prijave (*Application No.*):

P-200400022

(54) Naziv (*Title*):

Priprava amorfne pirolne spojine

Za izdajo tega potrdila je bila plačana taksa v višini 255,00 SIT po prvi alinei tarifne številke 4 taksne tarife Zakona o upravnih taksah (Uradni list RS, št. 8/00 in nadaljnji).

Ljubljana, 29.12.2004

Janez Milač
višji svrtovalec II

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ZAHTEVA ZA PODELITEV PATENTA

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Potrdilo o prejemu prijave
(izpolni urad)

Datum vložitve prijave: 23. 1. 2004

Številka prijave: P- 2004000 22

Žig urada in podpis:

2. Prijavitelj (priimek, ime in naslov, za pravne osebe firma in sedež):

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Priprava amorfne pirolne spojine

6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

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7. Dodatne zahteve:
- ☐ prijava je za patent s skrajšanim trajanjem
- ☐ predhodna objava patenta po preteku _____ mesecev
- ☐ prijava je izloèena iz prijave številka:

Prejeto dne: 23 -01- 2004	Osebna oddaja:
Podpis:	Oddano priporočeno dne:
Šifra:	Poštna številka: 1321

8. Izjava:
- ☐ izjava o skupnem predstavniku:

9. Priloge:
- ☒ opis izuma, ki ima _11_ strani 2x
- ☒ patentni zahtevek (zahtevki), ki ima(jo) _3_ strani; število zahtevkov: __13__ 2x
- ☒ skice (če so zaradi opisa izuma potrebne); število listov: _2_ 2x
- ☒ povzetek 2x
- ☐ potrdilo o plačilu prijavne pristojbine
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- ☐ prijava je bila predhodno posredovana po faksu ali v elektronski obliki
- ☐ _____

_____Cizerle Belčič Andreja_____
Priimek in ime ter podpis prijavitelja (zastopnika

Obrazec SIPO P 1

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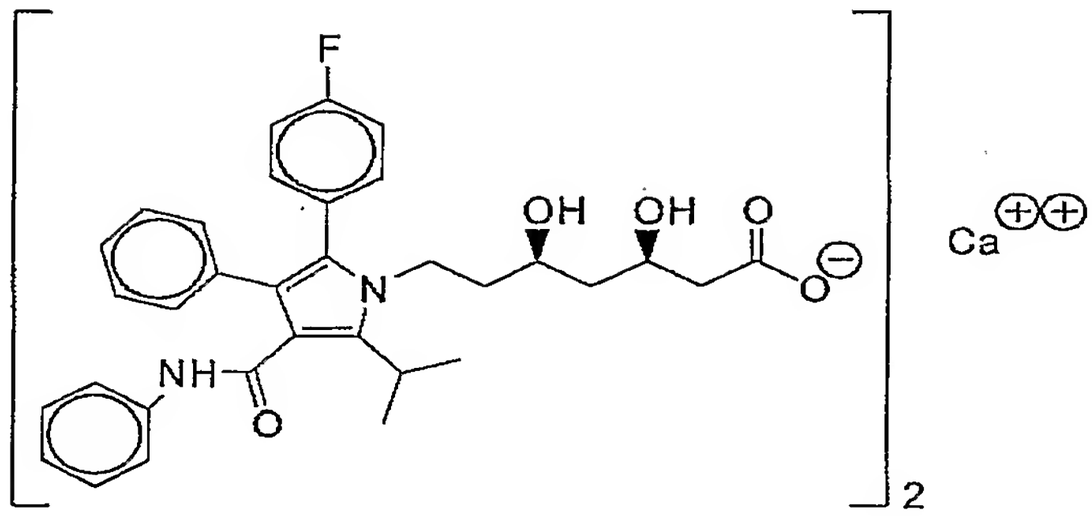
PROCESS FOR THE PREPARATION OF AMORPHOUS PYRROLE COMPOUND

Field of the Invention

The invention relates to a process of preparing amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester. This compound is a useful pharmaceutical intermediate in preparing atorvastatin calcium.

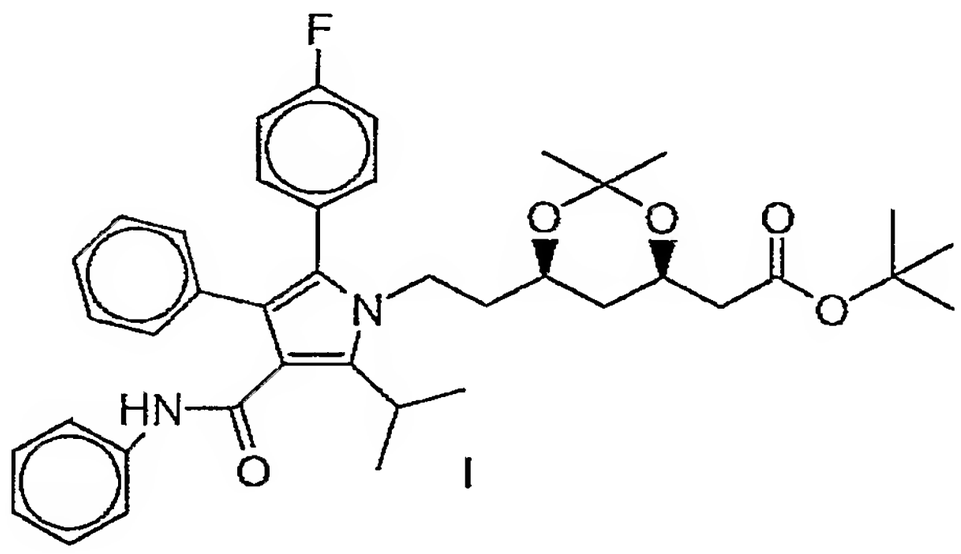
Technical Background

Atorvastatin calcium, a substance with the chemical name hemi calcium salt (R-(R*,R*))-2-(4-fluorophenyl)-β,δ-dihidroxy-5-(1-methylethyl)-3-phenyl-4-((phenylamino)carbonyl)-1H-pyrol-1-heptanoic acid and with the chemical formula



is an inhibitor of the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HM G-CoA reductase). This enzyme is the catalyst of intracellular synthesis of cholesterol. HM g-CoA reductase inhibitors are useful for treating dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary artery disease, coronary heart disease, vascular disorder, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease, abnormal bone states, amyloid-ß precursor protein processing disorders, such as Alzheimer's disease or Down's syndrome.

Substance (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester of the formula I



was first described in EP-B-330,172. The patent describes the process for the preparation of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester.

In many different literature pieces the process for the preparation of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, and further conversion thereof into atorvastatin calcium are described, such as *e. g.*, Tetrahedron Letters Vol. 33. Np. I7, 2283-2284 (1992), EP-A-553213, EP-A-643689, WO 02/043667, WO 02/059087, WO 02/083637, WO 02/083638, WO 03/016317, WO 03/082816.

WO 03/024959 relates to new crystalline forms I and II of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, and process of the preparation thereof.

Recently, a strong demand has arisen for pure and uniform products having physical properties appropriate for easily scaling-up procedure and use in industrial scale. It is very important that the starting compound (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester dissolves quickly and completely in aprotic solvents, while the first step in the synthesis of atorvastatin calcium is dissolution of said starting compound in an aprotic solvent. It is also desirable that the starting compound is pure and dry. Purer starting compound usually provides purer product.

When in large crystals some water is incorporated, this water cannot be removed therefrom during the drying process, *i.e.*, when the starting

compound is dissolved for the reaction to prepare atorvastatin, said incorporated water also dissolves in the solvent and, actually, a mixture of water and corresponding solvent for the dissolution of starting compound is obtained. Because water is not an appropriate solvent for organic compounds, *e. g.*, starting pyrrole compound for the synthesis of atorvastatin is practically insoluble in water, which results in the loss of starting compound or in increasing costs for the purification of mixture (filtering off insoluble material) and for an additional portion of solvent to fully dissolve the starting substance.

It is known from literature that pure crystalline products are generally less soluble (or they dissolve slowly), and that crystalline products are more difficult for purification in comparison to amorphous products. The reason for this is that a larger crystal in the crystalline product incorporates a larger amount of impurities and residual solvents during the crystal formation.

The solid formation process provides smaller particles of amorphous product. Because of the smaller surface and specific area the amorphous product occludes, adsorbs and absorbs a smaller amount of impurities, residual solvents and residual gases in comparison to the crystalline product. All objects mentioned above are important from the economical point of view, while at use of crystalline product, the purification phase requires additional recrystallization step.

This invention provides a process for the preparation of pure amorphous compound of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which can easily be used for preparing atorvastatin calcium. Amorphous starting compound in the synthesis of atorvastatin calcium has an advantage as far as better solubility and better purity.

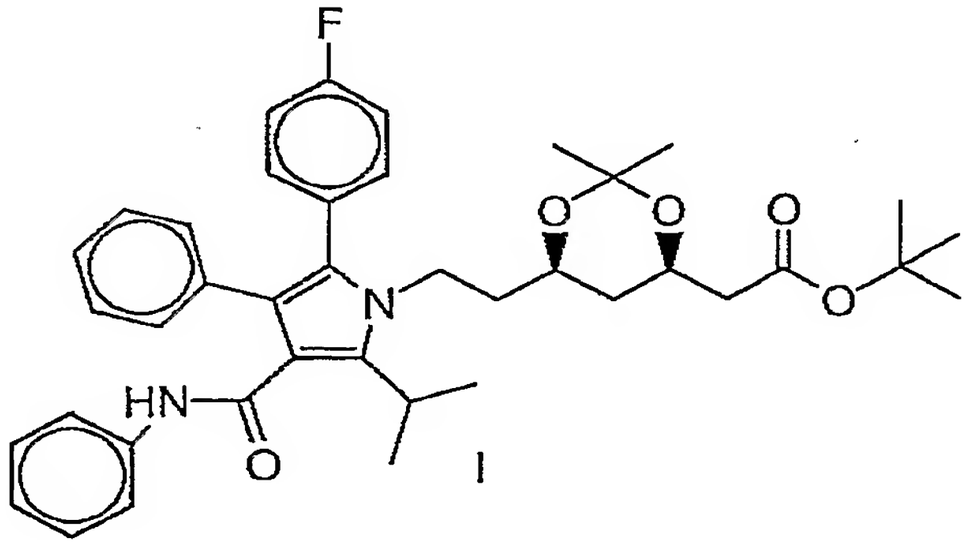
Description of the Drawings

Figure 1: An X-ray powder difractogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by Example 4.

Figure 2: DSC thermogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by Example 2.

Detailed Description of the Invention

As mentioned above, there exists a constant need for preparing amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester of formula I



I

which is the key intermediate in the synthesis of atorvastatin calcium. The main object of present invention is therefore providing a process for the preparation of amorphous compound of the formula I, that is used for preparing amorphous atorvastatin calcium. The described process is simple, and that is why it could easily be used for scaling-up and in industrial processes.

The first object of the invention is a process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester by dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, having undefined polymorph form, in an organic solvent as, *e. g.*, methanol, and concentrating the solution under normal or reduced pressure (reduced pressure scale from 1-5 mbar) at room or increased temperature up to 60 °C until the solution is absolutely clear. Thereafter, water is added to the solution to produce a precipitate of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester, which was further dried at reduced pressure (reduced pressure scale from 1-50 mbar) at increased temperature (up to 60 °C) to obtain the final product.

The second object of the invention is a process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester by dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester in an inert organic solvent, selected from the group consisting of methanol, acetonitrile,

chloroform, methylene chloride, acetone, toluene and tetrahydrofurane, at room or increased temperature up to 60 °C. The amount of solvent should be high enough to produce a completely clear solution. Then the solution is evaporated under normal or reduced pressure (reduced pressure scale from 1-5 mbar) at room or increased temperature (up to 60 °C) to completely remove the solvent from the mixture. Thereafter the residue is optionally dried at room or increased temperature (up to 60 °C) at normal or reduced pressure (reduced pressure scale from 1-50 mbar). The residue as formed is amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester.

A comparison between the solubility of amorphous and crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester shows that the amorphous product is better soluble in aprotic organic solvents, such as, *e. g.*, diisopropyl ether, methyl cyclohexane, and some other type of solvents, such as *e. g.*, isopropanol and lower alcohols. In the case of tetrahydrofurane, which is the key solvent in dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester for the atorvastatin synthesis, it was found that some dimness appeared if crystal form of the pyrrole compound was used, however, a perfectly clear solution was obtained if amorphous compound was used. Usually, when the solution (like in the case mentioned above) for the reaction is not clear, further purification (filtering, adding an active coal) should be performed to obtain a clear solution for the reaction and to avoid impurities in the final product. However, purification means additional costs and loss of time.

The following nonlimiting examples illustrate the present invention without limiting the scope of invention to said Examples.

Example 1: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5 g (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 100 ml methanol. The clear solution was concentrated at reduced pressure of 2 mbar to a point where the solution was still totally clear, *i.e.*, to a volume of approximately 20 ml. Then 200 ml of water were added to form amorphous product. The precipitation was filtered out and dried at reduced pressure of 50 mbar at 60 °C for 5 hours. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 4.46 g.

Example 2: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5 g (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 100 ml acetonitrile. The clear solution was dried at reduced pressure of 2 mbar at 60 °C until a completely dry product was obtained. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5 g.

Example 3: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5 g (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 10 ml methylene chloride. The clear solution was dried at reduced pressure of 2 mbar at 60 °C until a completely dry product was obtained. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5 g.

Example 4: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5 g (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 5 ml chloroform. The clear solution was allowed to stand without cover at room temperature for 5 hours or long enough to completely evaporate solvent from the material. After that the residue was dried at reduced pressure of 50 mbar for 5 hours at 50 °C. The yield of the amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5 g.

Example 5: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5 g (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 5 ml chloroform. The clear solution was dried at reduced pressure of 2 mbar at 60 °C until a completely dry product was obtained. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5 g.

Example 6: X-ray powder diffraction analysis of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

Amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by Example 4 has an X-ray powder difractogram substantially as shown in Figure 1.

The X-ray powder diffraction pattern was collected on a Philips PW1710 difractometer in reflection geometry. The instrument was regularly calibrated with silicon standard. A standard Philips back-loading sample holder was used. Sample storage, mounting, and data collection were performed at room temperature. Instrumental parameters were: CuK_α radiation (30 mA, 40 kV, λ = 1.5406 Å, variable divergence slit (approx. 12 × 16 mm irradiated area),

0.4 mm receiving slit, graphite monochromator on the secondary side, scintillation counter. Data collection parameters were: 2θ range from 4 ° to 37 °, step scan mode in steps of 0.04 ° 2θ, integration time 1 second at each step.

Example 7: DSC analysis of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

The DSC (Differential Scanning Calorimetry) analysis was performed on an Mettler Toledo DSC822e analyzer. Measurement was performed in an unsealed Al pan with a heating rate of 5 K/min. The heating interval was 40-160 °C. The thermogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by Example 2 is expressed in Figure 2.

The DSC curve shows the thermal transformation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester into crystalline forms. In the DSC curve there is clearly seen the formation of crystals of Form II at around 120 °C and melting point of these crystals at 136 °C.

Claims

1. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent, and isolation of an amorphous product.

2. The process according to claim 1, wherein an organic solvent is methanol.

3. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises:
   a) dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent,
   b) concentrating the solution,
   c) adding water,
   d) precipitating the amorphous product.

4. The process according to claim 3, wherein an organic solvent is methanol.

5. The process according to claim 3, wherein the concentration of solution is performed at reduced pressure to a point where the solution is clear.

6. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent, and isolation of an amorphous product.

7. The process according to claim 6, wherein an inert organic solvent is selected from the group consisting of methanol, acetonitrile, chloroform, methylene chloride, acetone, toluene or tetrahydrofurane.

8. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises

   a) dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent,
   b) isolation of the amorphous product.

9. The process according to claim 8, wherein the dissolving of crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic

acid - tertiary butyl ester in an inert organic solvent is performed at room temperature or under heating up to 60 °C.

10. The process according to claim 8, wherein an inert organic solvent is selected from the group consisting of methanol, acetonitrile, chloroform, methylene chloride, acetone, toluene or tetrahydrofurane.

11. The process according to claim 8, wherein the isolation of the amorphous product comprises evaporating the solvent at room or increased temperature at normal or reduced pressure.

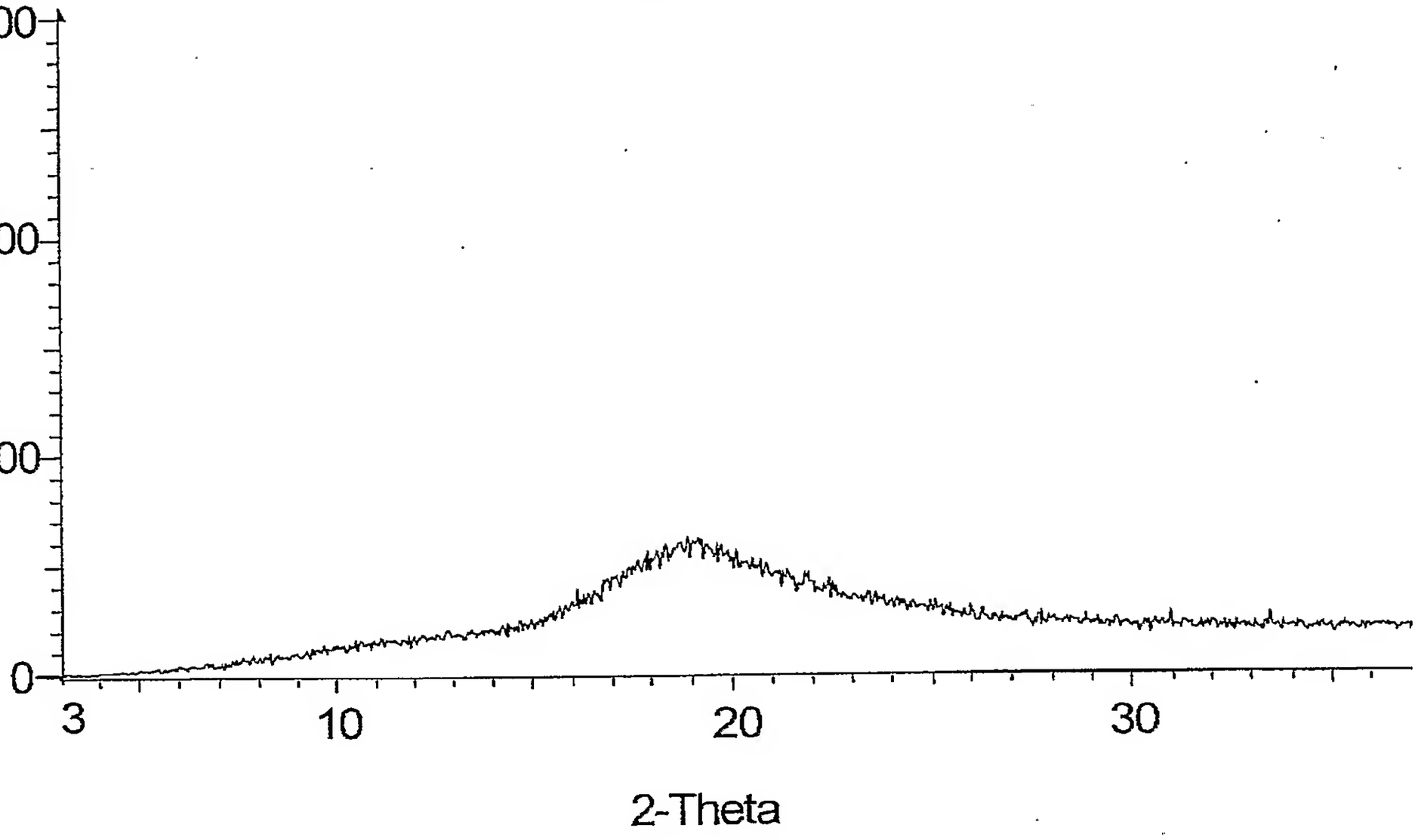
12. Amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester having an X-ray powder difractogram substantially as shown in Figure 1.

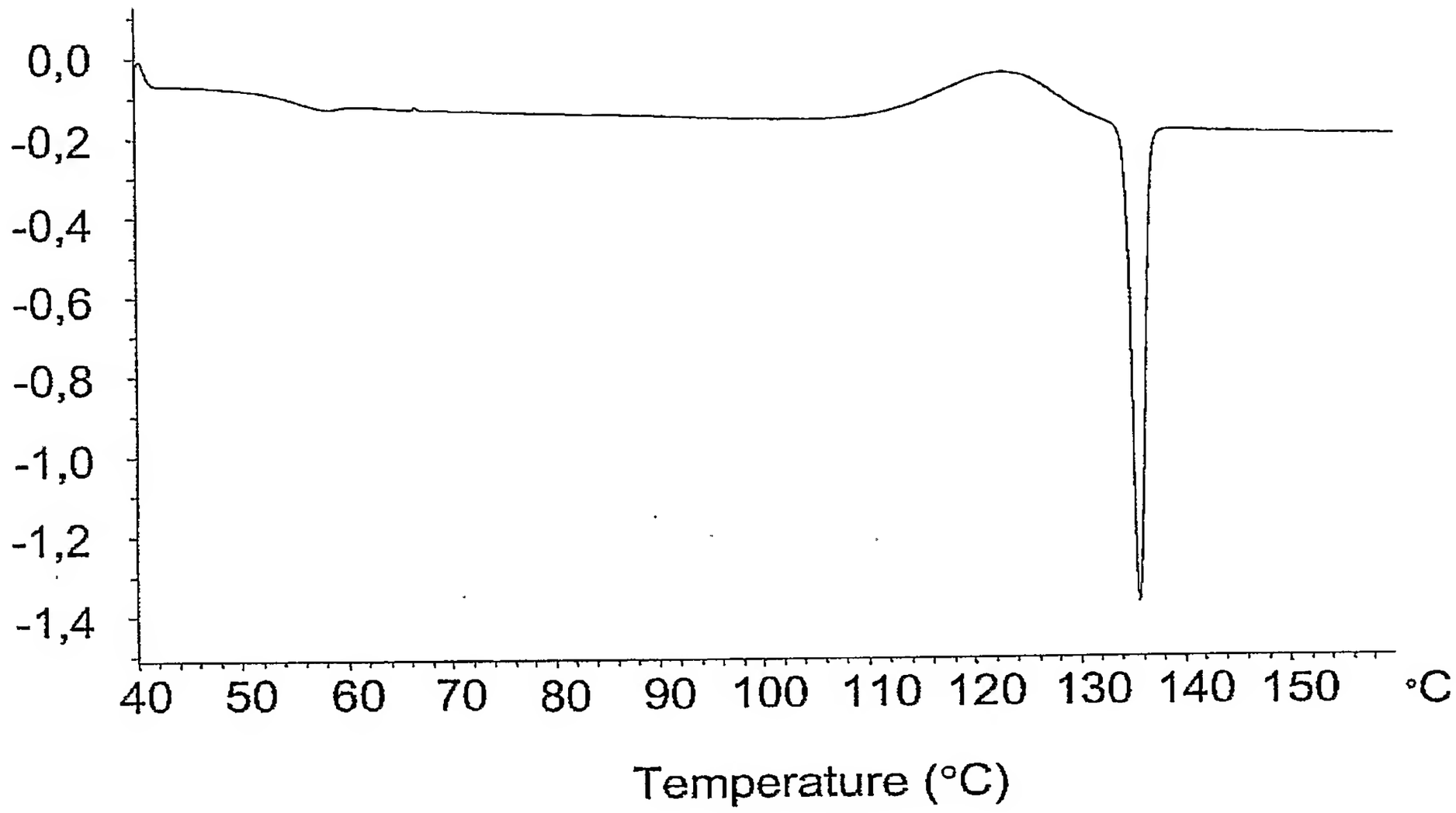
13. Amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester having a DSC thermogram substantially as shown in Figure 2.

Abstract

The invention relates to a process of preparing amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester which is a useful pharmaceutical intermediate in preparing atorvastatin calcium.

1/2

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-0,4
-0,6
-0,8
-1,0
-1,2
-1,4
40
50
60
70
80
90
100
110
120
130
140
150
°C
Temperature (°C)